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REVIEW

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The urea-to-creatinine ratio as an emerging biomarker in critical care: a scoping review and meta-analysis

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Abstract

Background Severe protein catabolism is a major aspect of critical illness and leads to pronounced muscle wasting and, consequently, extended intensive care unit (ICU) stay and increased mortality. The urea-to-creatinine ratio (UCR) has emerged as a promising biomarker for assessing protein catabolism in critical illness, which is currently lacking. This review aims to elucidate the role of UCR in the context of critical illness.

Methods This scoping review adhered to the PRISMA Extension for Scoping Reviews guidelines. A comprehensive literature search was conducted on the 3rd of September 2024, across Embase, PubMed, ScienceDirect, and Cochrane Library to identify studies related to (1) critically ill adult patients and (2) reporting at least a single UCR value. A meta-analysis was conducted for ≥ 5 studies with identical outcome parameters.

Results Out of 1,450 studies retrieved, 47 were included in this review, focusing on UCR's relation to protein catabolism and persistent critical illness (10 studies), mortality (16 studies), dietary protein interventions (2 studies), and other outcomes (19 studies), such as delirium, and neurological and cardiac adverse events. UCR is inversely correlated to muscle cross-sectional area over time and associated to length of ICU stay, emphasising its potential role in identifying patients with ongoing protein catabolism. A UCR (BUN-to-creatinine in mg/dL) of ≥ 20 (equivalent to a urea-to-creatinine in mmol/L of approximately 80) upon ICU admission, in comparison with a value < 20, was associated with a relative risk of 1.60 (95% CI 1.27–2.00) and an adjusted hazard ratio of 1.29 (95% CI 0.89–1.86) for in-hospital mortality.

Discussion UCR elevations during critical illness potentially indicate muscle protein catabolism and the progression to persistent critical illness, and high levels at ICU admission could be associated with mortality. UCR increments during ICU stay may also indicate excessive exogenous dietary protein intake, overwhelming the body's ability to use it for whole-body or muscle protein synthesis. Dehydration, gastrointestinal bleeding, kidney and liver dysfunction, and renal replacement therapy may also influence UCR and are considered potential pitfalls when assessing catabolic phases of critical illness by UCR. Patient group-specific cut-off values are warranted to ensure its validity and application in clinical practice.

Keywords Critical illness, Protein catabolism, Nutrition, Intensive care unit, UCR, Urea-to-creatinine ratio

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Introduction

Critically ill patients are in a catabolic state due to extensive inflammation, neurohumoral changes, and prolonged immobilisation. When ongoing, protein catabolism may lead to significant muscle wasting and consequent weakness [1–3], resulting in prolonged ICU stay [4, 5] and increased risk of long-term disability or death [3, 5–7]. Existing biomarkers to monitor muscle wasting during critical illness are often complex and expensive, and more diagnostic accuracy is needed to accurately capture the full extent of catabolic activity [8, 9]. Therefore, identifying a reliable and standardised biomarker that can be easily measured and monitored is essential to detect and monitor ongoing catabolism in critically ill patients.

The urea-to-creatinine ratio (UCR), the quotient of (blood) plasma urea (nitrogen) over creatinine, may be a useful biomarker of overall protein catabolism in critically ill patients [10, 11]. Urea, produced in the liver as a by-product of protein breakdown, rises in the blood during catabolic states due to heightened proteolysis [8]. Although elevated plasma urea reflects overall protein breakdown, skeletal muscle represents the largest protein reservoir in the body [12, 13] and ICU patients undergo extensive skeletal muscle wasting during periods of severe illness [1]. Therefore, increments in plasma urea are likely to be related to the extent of muscle atrophy during critical illness, in addition to exogenous protein provision. Simultaneously, creatinine production decreases primarily due to the reduction in absolute skeletal muscle mass, as serum creatinine is mainly a breakdown product of muscle creatine phosphate. The combination of increased urea and decreased creatinine results in a rise in UCR. As such, this may indicate significant protein catabolism, often seen in stress, infection, or corticosteroid use [8]. Accordingly, an elevated UCR may serve as a potential indicator of muscle wasting, reflecting both the increased breakdown of muscle proteins and the reduction in muscle mass [8, 14].

Although urea and creatinine are frequently monitored in ICUs, the clinical potential of UCR is frequently under-recognised, and its broader utility in managing critical illness remains largely unexplored. In addition to its role as a marker for the end products of protein catabolism, Gunst et al. proposed that the UCR could be used to monitor the catabolic process of muscle proteins during critical illness [8]. This may enable the modification of dietary regimens and the introduction of therapeutic measures before the discernment of alterations in muscle mass and functionality. Prior research has demonstrated that a high UCR may be indicative of an excess of exogenous amino acids, in addition to endogenous catabolism [15, 16], suggesting that the supply of dietary protein may exceed the body's capacity for utilisation at that moment. This phenomenon is known as anabolic resistance, the reduced ability of muscle tissue to synthesize protein in response to anabolic stimuli like dietary protein or exercise [17]. This condition is driven by inflammation, insulin resistance, and physical inactivity [17]. These mechanisms reduce the effectiveness of key pathways like mTOR signalling, contributing to muscle loss and functional decline, particularly in aging, chronic disease, and critical illness [17, 18].

The finding that UCR may reflect anabolic resistance and even harm by high protein dosing is also corroborated by the reanalysis of the EFFORT protein trial, indicating that the elevated risk of mortality observed in critically ill patients randomised to a higher protein dose may be attributed to extensive ureagenesis [19]. Conversely, a low or declining UCR could serve as a marker for protein-responsive ICU patients [20].

There is an increasing need for personalised nutrition to provide optimal nutrition dose and timing for critically ill patients [21], a necessity that experts in a consensus paper have also acknowledged [22]. In this context, the bedside biomarker UCR could prove useful in determining the extent, timing, and variability of anabolic responses, particularly as anabolic resistance resolves and the state shifts toward improved metabolic responsiveness to feeding.

This scoping review elucidates the roles of UCR in the context of critical illness. It aims to investigate the role of UCR as a potential biomarker of muscle wasting and indicator for persistent critical illness, the association of UCR and mortality in critically ill patients, the potential of UCR as a biomarker in response to nutrition interventions, and understand any other roles of UCR in critical illness. Furthermore, this scoping review highlights the pitfalls of interpreting UCR values, delineates areas of current knowledge deficiency, and offers recommendations for enhancing critical care.

Methods

This scoping review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Extension for Scoping Reviews guidelines [9], with the study protocol registered on the 28 th of August 2024, on the Open Science Framework (https://doi.org/10.17605/OSF.IO/M365Q). A literature search was conducted on the 3rd of September 2024, across multiple databases, including Embase, PubMed, ScienceDirect, and the Cochrane Library, to identify relevant studies on UCR in critically ill patients. The primary search terms included'critical illness,"UCR,'and related variations (Additional file 1: Table S1). No restrictions were applied regarding publication year and status.

Articles were included if they focused on (1) critically ill adult patients (age ≥18 years) and 2() UCR in any context (as descriptive or outcome measure). No restrictions were placed on geographical location, patient race, sex, or the type of critical care facility. All identified articles were imported into Rayyan, an online tool for conducting systematic reviews, where duplicates and triplicates were manually identified and removed [23]. Two authors (MCP & AvE) independently screened the remaining articles based on their titles and abstracts. Full texts of the selected articles were then obtained for further review. If full texts were unavailable, authors were contacted for access. Studies were excluded if (1) they did not include data specifically related to critically ill patients, (2) only a case report, symposium abstract, or editorial was available, and 3) the study was in a foreign language with no available translation. Additional articles were identified using the included studies'relevant search terms and reference lists. The full-text screening was conducted independently by two authors (MCP & AvE). In cases of disagreement, they discussed the issue to reach a consensus. In cases where consensus could not be reached, an adjudicator made the final decision (AvZ). Data was extracted independently by two authors (MCP & AvE), abstracted data including year of publication, country of origin, population and sample size, sex distribution, inclusion/exclusion criteria, methodology, outcome measures, and key findings are summarised in Table 1, 2, 3 and Additional file 1: Table S3. Only studies that met the criteria of comparing two UCR groups were included in the post-hoc meta-analysis. When possible, two groups were constructed based on the available data, with the classification of these groups being determined by the cut-off value as reported in the article. In instances where multiple groups were presented and their integration into two groups was possible, the cut-off value that corresponded most closely to a BUN/Cr ratio of 20 was selected to ensure the comparability of the results with those of other studies. The quality of the included studies was evaluated using the JBI Critical Appraisal Tools [24], with higher scores indicating a higher study quality.

In this review, the term UCR is used to refer to both the blood urea nitrogen (BUN)-to-creatinine ratio and the urea-to-creatinine ratio due to both measurements being reported as UCR in the studies under review. If values are referenced in the review, they pertain to the BUN-to-creatinine ratio in mg/dL:mg/dL, unless otherwise indicated. In instances where five or more studies employed the same outcome measure and sufficient event data were available to calculate risk ratios, post-hoc meta-analyses were conducted with a random effects model using R Studio version 2023.06.1 and R version 4.4.1 and presented in forest plots. Heterogeneity was quantified using the I^2 measure, and a *P*-value < 0.05 was considered statistically significant. The established cut-off values for UCR were maintained, as presented in the original studies, with the UCR cut-off value illustrated in the meta-analysis. In cases where multiple cut-off values were reported, the one most consistent with the other studies was used.

Results

A total of 1,450 studies were initially identified in the search, with 140 selected after title and abstract screening (Additional file 1: Table S1). Additional file 1: Fig. S1 and Table S4 present the exclusion criteria for full-text articles. After a comprehensive review with 94% initial consensus during the independent review process, 47 articles investigating UCR in critically ill patients were included. These studies focused primarily on the following areas: 10 on muscle wasting and persistent critical illness (Table 1), 17 on mortality (Table 2), two on protein interventions (Table 3), and 19 on other roles (Additional file 1: Table S3). A critical appraisal checklist for the included studies is provided in Additional file 1: Table S2.

UCR as indicator of catabolism

Two studies have been conducted to determine the relationship between UCR and muscle mass (Table 1). A study by Haines et al. among 1173 ICU patients after major trauma found no correlation between muscle cross sectional area (CSA) measured on L3 and L4 level on Computed Tomography (CT) and UCR at ICU admission. However, it was observed that the group with an ICU stay ≥10 days had increased UCR from ICU admission to discharge compared to those discharged from the ICU before day 10 (133% vs. 59%, $p < 0.001$) [14]. In patients with persistent critical illness, a negative correlation was observed between UCR and muscle CSA after day 10 (L4 psoas and L3 muscle CSA R^2 0.39 and 0.44, respectively, both $p < 0.001$). This correlation consisted of a median decrease of 34% in the L4 psoas CSA and a 21% decrease in the L3 muscle CSA, with a concomitant 221% increase in UCR (from urea-creatinine-ratio 51 mmol/L: mmol/L [44–67] to 164 mmol/L: mmol/L [109–200], p < 0.001). Additionally, in a single centre retrospective investigation in mixed medical-surgical ICU patients it was observed that UCR during the first three days of ICU admission was higher in medical patients with persistent critical illness ($n = 250$) compared to those without ($n = 862$), but no difference was found in UCR trajectory in the trauma subpopulation [25]. However, Araújo et al. found no statistically significant association between UCR and reduced calf circumference in 208 Coronavirus disease 2019 (COVID-19) ICU patients (OR 1.01, 95% CI 0.99–1.03, $p = 0.194$), but the dynamics of UCR and calf

Table 1 Role of UCR as a catabolic marker and indicator for persistent critical Illness

Title	Author(s)	Year	Country	Population & Sample Size	Sex Distribution	Inclusion/ Exclusion Criteria	Methodology	UCR	Outcome Measures	Key Findings
	Catabolism									
Association of Calf Circumference with Clinical and Biochemical Markers in Older Adults with COVID-19 Admitted at Intensive Care Unit: A Retrospective Cross-Sectional Study [26]	Araújo, V. A., Souza, J. S., Giglio, B. M., Lobo, P. C. B., & Pimentel, G. D	2024	Brazil	208 older adults (≥ 60 years) with COVID-19 admitted to ICU	113 = M, 95 = F	Inclusion: COVID-19 was confirmed by reverse transcription polymerase chain reaction or CT, and ICU stay ≥ 24 h. Exclusion: Palliative care, incomplete anthropometric data	A retrospective cross-sectional study was conducted using Pearson's correlation and Cox regression model, adjusted for age, sex, and BMI	Urea/Cr (mg/dL: mg/dL); measured according to the hospital's routine from ICU admission (timing not specified)	Calf circumference (CC; adjusted for BMI)	1. Association of UCR between reduced and normal calf circumference groups (reduced group higher UCR), which continued only for men after stratification by sex 2. In the regression model, no association was found after adjusting for sex, age, and BMI
Elevated urea-to-creatinine ratio provides a biochemical signature of muscle catabolism and persistent critical illness after major trauma [14]	Haines, R. W., Zolfaghari, P., Wan, Y., Pearse, R. M., Puthucheary, Z., & Prowle, J. R	2019	UK	1173 trauma ICU patients	945 = M, 228 = F	Inclusion: ICU trauma survivors ≥ 10 days. Exclusion: Patients with advanced kidney disease (Cr > 354 µmol/L), deaths within 24 h, and patients on RRT	Retrospective analysis comparing UCR, muscle mass decline, and ICU stay in trauma patients, with a validation cohort from the MIMIC-III database	Urea/Cr (mmol/L: mmol/L); collected daily from ICU admission until discharge; first result in each 24-h period recorded per patient	Muscle cross-sectional area (CSA, L3 and L4 CT) and development of persistent critical illness (PCI); ICU stay ≥ 10 days	1. UCR increased in patients with and without PCI, but median values more than doubled by day 10 in patients with PCI compared to a modest rise and then progressive fall in those discharged by day 10 2. UCR and muscle CSA showed no correlation at ICU admission, however they negatively correlated in patients with PCI

Table 1 (continued)

Title	Author(s)	Year	Country	Population & Sample Size	Sex Distribution	Inclusion/ Exclusion Criteria	Methodology	UCR	Outcome Measures	Key Findings
Obesity attenuates inflammation, protein catabolism, dyslipidaemia, and muscle weakness during sepsis, independent of leptin [27]	Vankrunkelsven, W., Derde, S., Gunst, J., Vander Perre, S., Declerck, E., Pauwels, L., Derese, I., Van den Berghe, G., & Langouche, L	2022	Belgium	1388 ICU patients	842 = M, 546 = F	Inclusion: Critically ill patients, ICU stay ≥ 5 days with available nitrogen balance data	Post hoc analysis of the EPaNIC study, propensity score matching, matching patients with BMI < 25 and BMI ≥ 25	Plasma Urea/Cr (mg/dL: mg/dL); collected on ICU day 5	Protein catabolism (plasma UCR (Urea/Cr, mg/dL: mg/dL) and nitrogen balance)	1. On day 5 of ICU stay, critically ill patients with a BMI ≥ 25 exhibited lower net protein catabolism than those with a BMI < 25, as evidenced by a reduced net nitrogen loss and a lower urea-to-creatinine ratio
Value of the urea/creatinine index in isolated urine to estimate severe protein hypercatabolism in ventilated patients [79]	Moretti, D., Ré, M. D., Rocchetti, N. S., Bagilet, D. H., Settecase, C. J., Buncuga, M. G., & Quaglino, M. B	2020	Argentina	52 ICU patients (ventilated)	35 = M, 17 = F	Inclusion: Patients 18 years or older, ICU stay ≥ 72 h, receiving assisted mechanical ventilation. Exclusion: Patients with renal insufficiency or on RRT	Prospective observational study measuring UCR in isolated urine at two time points (day 2 and day 4). Total urinary nitrogen was used as the gold standard to estimate protein catabolism	Urine Urea/Cr; collected on ICU day 1 (from admission to 8 a.m.), day 2 (T1), and day 4 (T2) at 8 a.m	Severe protein hypercatabolism, defined as total urinary nitrogen > 15 g/day	1. UCR on day 4 had a significant correlation with severe protein hypercatabolism (p = 0.032), UCR on day 2 was not significant (p = 0.255) 2. UCR had a sensitivity of 79.31% and specificity of 60.87% for detecting severe protein hypercatabolism on day 4, with a cut-off value of 16.15 3. The authors suggest that UCR may be useful for screening severe protein hypercatabolism but cannot replace total urinary nitrogen measurement
UCR at Admission and Length of Stay										

Table 1 (continued)

Title	Author(s)	Year	Country	Population & Sample Size	Sex Distribution	Inclusion/ Exclusion Criteria	Methodology	UCR	Outcome Measures	Key Findings
Blood Urea Nitrogen: Creatinine ratio at admission to predict hospital stay duration in decompensated heart failure patients at a tertiary care hospital in rural Puducherry, India [80]	Ravi, S., Selvamuthukumaran, S., & Sakthivel, V	2023	India	40 ICU patients with decompensated heart failure	25 = M, 15 = F	Inclusion: ICU patients (age ≥ 18) diagnosed with heart failure as per Framingham criteria. Exclusion: Chronic kidney disease, pregnancy, malignancies, diuretic or ACE inhibitor use	A prospective observational study conducted over 18 months. Baseline characteristics collected on admission	BUN/Cr (mg/dL: mg/dL); collected at hospital admission	Duration of hospital stay	1. UCR at hospital admission was not significantly associated with the duration of hospital stay in patients with heart failure
The relationships between routine admission blood tests and burn size, and length of stay in the intensive care unit [28]	Yeong, E.-K., Tung, K.-Y., Chang, C.-H., & Tsai, S.-J	2022	Taiwan	73 patients admitted to ICU with severe burns (of which 62 patients with burns > 20% of the total body surface area (ICU criteria)	31 = M, 42 = F	Inclusion: Patients admitted with burns after corn starch dust explosion incident (the 27 th of June in 2015). Exclusion: no available blood test < 24 h after admission	Retrospective study analysing the relationship between UCR and burn size, as well as ICU length of stay (ICU LOS) in critically ill burn patients	BUN/Cr (mg/dL: mg/dL); collected at ICU admission	Disease severity (burn size and ICU stay)	1. Increased UCR was positively correlated with longer ICU stay and higher disease severity in female patients (each unit increase in UCR; 1.2 days increase ICU LOS), but not in male patients
The course of UCR during Persistent Critical Illness										
Defining persistent critical illness based on growth trajectories in patients with sepsis [10]	Zhang, Z., Ho, K. M., Gu, H., Hong, Y., & Yu, Y	2020	USA	22,868 patients with sepsis	11,240 = M, 11,628 = F	Inclusion: Patients with sepsis were admitted to the ICU based on Sepsis-3 criteria, documented infection, and SOFA score > 2. Exclusion: Patients with ICU stay < 2 days or without complete data	A retrospective cohort study using latent growth mixture modelling was used to identify classes based on SOFA scores. Biochemical markers, including UCR, were assessed for their predictive value	BUN/Cr (mg/dL: mg/dL); collected daily from ICU admission to day 10	Development of persistent critical illness (PCI); definition based on models and ICU and hospital length of stay (LOS)	1. UCR was significantly higher in patients who developed PCI ($p < 0.05$) 2. Elevated UCR was linked to higher SOFA scores and a prolonged ICU stay

Table 1 (continued)

Title	Author(s)	Year	Country	Population & Sample Size	Sex Distribution	Inclusion/ Exclusion Criteria	Methodology	UCR	Outcome Measures	Key Findings
ICU-acquired hypernatremia is associated with persistent inflammation, immunosuppression and catabolism syndrome [29]	Rugg, C., Strohle, M., Treml, B., Bachler, M., Schmid, S., & Kreutziger, J	2020	Austria	115 ICU patients	75 = M, 40 = F	Inclusion: ICU patients with sufficient renal function and ICU stay ≥ 14 days. Exclusion: Patients with renal dysfunction or incomplete data	Retrospective single-centre study comparing patients with ICU-acquired hypernatremia to those without, focusing on catabolic biomarkers	Urea/Cr (mg/dL: mg/dL); collected daily from ICU admission to day 21	Length of ICU stay and hypernatremia, defined as sodium level > 145	1. Compared to ICU admission or patients discharged earlier, those with prolonged lengths of stay showed a significant increase in this ratio (greater than 75 mg/dL) 2. Significantly higher UCR in the group with hypernatremia
Mid-Term Evolution of the Serum Acylcarnitine Profile in Critically Ill Survivors: A Metabolic Insight into Survivorship [30]	Rousseau, A.-F., Ngongan, A., Colson, C., Minguet, P., Neis-Gilson, S., Cavalier, E., Minguet, G., Misset, B., & Boemer, F	2023	Belgium	64 ICU survivors	44 = M, 20 = F	Inclusion: ICU stay ≥ 7 days, follow-up at 3 months post-ICU discharge. Exclusion: Patients with end-of-life conditions or those on L-carnitine supplementation	A prospective observational study assessing acylcarnitine profiles and metabolic biomarkers over 3 months post-ICU	Urea/Cr (mg/dL): mg/dL; collected at T0 (post-ICU ward visit) & M3 [3 months post-discharge]	Sarcopenic Index	1. UCR decreased significantly between T0 (immediately post-ICU) and M3 (3 months post-ICU) ($p = 0.008$), whilst the Sarcopenic Index increased

Table 1 (continued)

Title	Author(s)	Year	Country	Population & Sample Size	Sex Distribution	Inclusion/ Exclusion Criteria	Methodology	UCR	Outcome Measures	Key Findings
Time course of plasma urea and urinary urea excretion in patients with a prolonged ICU stay [12]	Zijlstra, H. W., Westland, G. J., Volbeda, M., van Meurs, M., Pillay, J., Franssen, C. F. M., Stegeman, C. A., & Nijsten, M. W	2024	Netherlands	638 ICU patients	495 = M, 143 = F	Inclusion: Patients with an ICU stay ≥ 28 days, complete data on plasma and urinary urea and creatinine Exclusion: Patients with acute kidney injury (AKI) stage 3 or incomplete data	A prospective observational cohort study measured plasma urea, urinary urea excretion, and urinary creatinine excretion over 30 days in ICU patients	Plasma Urea/Cr (mmol/L:mmol/L) and urinary Urea/Cr; collected daily from ICU admission to day 20	Plasma UCR (Urea/Cr, mmol/L:mmol/L), urinary UCR (Urea/Cr)	1. Plasma and urinary UCR (plasma UCR and urinary UCR) increased during the entire ICU stay, with the highest increase in the first seven days of the stay 2. Urinary and plasma UCR showed a similar course 3. The plasma UCR was significantly higher in female patients than in male patients, but the course over time did not differ between males and females ($p < 0.001$)

Table 1 (continued)

Title	Author(s)	Year	Country	Population & Sample Size	Sex Distribution	Inclusion/ Exclusion Criteria	Methodology	UCR	Outcome Measures	Key Findings
Urea to creatinine ratio as a predictor of persistent critical illness [25]	Statlender, L., Shochat, T., Robinson, E., Fishman, G., Hellerman-Itzhaki, M., Bendavid, I., Singer, P., & Kagan, I	2024	Israel	2098 ICU patients	PCI Group: 324 = M 156 = F; Non-PCI group: 990 = M, 628 = F	Inclusion: ICU patients Exclusion: Patients who died within 10 days, were admitted with creatinine > 4 mg/dL, and were treated with RRT during ICU stay	Retrospective single-centre cohort study. Patients were grouped based on ICU length of stay, > 10 days (persistent critical illness; PCI group) or not (no-PCI group)	Urea/Cr (mg/dL: mg/dL); using the first lab result from each ICU day	90-day and 1-year mortality	1. UCR was significantly higher in PCI patients compared to no-PCI patients on the first day of admission, a median of 44 vs 41 (p = 0.0313) respectively. However, the differences in UCR between PCI and no-PCI groups were not significant after day 1, except for medical patients on day 2 and 3 2. No differences were observed in UCR between PCI and no-PCI patients in different KDIGO stages

The following table provides an overview of studies that have examined the role of UCR (urea-to-creatinine ratio) as a catabolic marker and indicator for persistent critical illness. The table focuses on UCR and the most relevant inclusion and exclusion criteria; other possible study outcomes unrelated to UCR are not described. The table reports whether the studies used blood urea nitrogen to creatinine (BUN/Cr) ratios or urea-to-creatinine ratios, both of which are encompassed under the term UCR. Furthermore, in the event of a reported value, the unit of measurement utilised in the UCR is explicitly stated (mg/dL: mg/dL or mmol/L: mmol/L). For details regarding unit conversion, see Fig. 4. *AKI* acute kidney injury, *BMI* body mass index, *CT* computed tomography, *COVID-19* Coronavirus Disease 2019, *F* female, *ICU* intensive care unit, *ICU LOS* intensive care unit length of stay, *KDIGO* kidney disease improving global outcomes, *M* male, *RRT* renal replacement therapy, *SOFA* sequential organ failure assessment, *Urea/Cr/UCR* urea-to-creatinine ratio

Table 2 Summary of included articles assessing the impact of UCR on mortality risk in critically Ill patients

Title	Author(s)	Year	Country	Population & Sample Size	Sex Distribution	Inclusion/ Exclusion Criteria	Methodology	UCR	Covariates Included	Outcome Measures	Key Findings
	In-hospital mortality										
A Prediction Model for Assessing Prognosis in Critically Ill Patients with Sepsis-associated Acute Kidney Injury [57]	Hu, H., Li, L., Zhang, Y., Sha, T., Huang, Q., Guo, X., An, S., Chen, Z., & Zeng, Z	2021	China	2,168 ICU patients [2, 066 in the training cohort, 102 in the validation cohort]	1,223 M, 843 F	Inclusion: Critically ill patients with sepsis-associated acute kidney injury. Exclusion: Patients < 18 years, ICU stay < 48 h, missing data for key variables	Retrospective cohort analysis, multivariable Cox regression-based model	BUN/Cr, (mg/dL: mg/dL); worst values within 24 h of ICU admission	Not reported	In-hospital mortality	1. Higher UCR (> 20) was significantly associated with increased in-hospital mortality (HR:1.62, 95% CI: 1.30–2.02)
Association between BUN/creatinine ratio and the risk of in-hospital mortality in patients with trauma-related acute respiratory distress syndrome: a single-centre retrospective cohort from the MIMIC database [56]	Ma, H., Lin, S., Xie, Y., Mo, S., Huang, Q., Ge, H., Shi, Z., Li, S., & Zhou, D	2023	China	1,034 ICU patients	583 M, 451 F	Inclusion: ICU patients from the MIMIC-III database, adults with trauma-related acute respiratory distress syndrome. Exclusion: ICU stay < 24 h, heart failure, advanced kidney dysfunction (serum creatinine > 354 µmol/L), onychomycosis severity index > 315 mmHg, missing data UCR	A retrospective cohort study was conducted using data from the MIMIC-III database, using multivariable Cox regression	BUN/Cr, (mg/dL: mg/dL); collected first 24 h after ICU admission	Ajusted for gender, ethnicity, length of stay in ICU, vasopressor use, ECI, NEUT, HB, RDW, lactate, SAPS- II, SOFA score and RTS	In-hospital mortality	1. Higher UCR was associated with increased in-hospital mortality risk compared to a UCR < 15.54 (UCR 15.54–21.43 HR: 2.00 (95% CI: 1.18–3.38) and UCR > 21.43 HR: 1.76 (1.04–2.99)) 2. The predictive performance of UCR was superior to single BUN or creatinine

Table 2 (continued)

Title	Author(s)	Year	Country	Population & Sample Size	Sex Distribution	Inclusion/ Exclusion Criteria	Methodology	UCR	Covariates Included	Outcome Measures	Key Findings
Association between serum osmolality and risk of in-hospital mortality in patients with intracerebral haemorrhage [81]	Hu, Z., & Sha, Q	2024	China	1,837 ICU patients	1,004 M, 833 F	Inclusion: ICU patients from the MIMIC-IV database, adults aged ≥ 18 with intracerebral haemorrhage. Exclusion: No osmolality data, ICU stay < 24 h	Retrospective cohort study using MIMIC-IV database data. Multivariable Cox regression model	BUN/Cr, (mg/dL: mg/dL); timing of collection not specified	Adjusted for age, race, insurance, marital status, MAP, respiratory rate, urine output-24 h, AKI, SAPSII, SOFA, GCS, CCI, ICU type, ventilation, vasopressor, diuretic, mannitol, brain surgery, platelet, RDW, hemoglobin, hematocrit, bicarbonate, and eGFR	In-hospital mortality	1. BCR > 20 compared to ≤ 20 was not significantly associated with in-hospital mortality after adjustment analysis by age, gender, and AKI status. (HR: 1.17 (95% CI: 0.95–1.45), p = 0.142) 2. The univariable Cox regression model found a correlation between BCR > 20 compared to ≤ 20 and in-hospital mortality (HR = 1.42, p = 0.001)
Association between the blood urea nitrogen to creatinine ratio and in-hospital mortality among patients with acute myocardial infarction: A retrospective cohort study [37]	Huang, S., Guo, N., Duan, X., Zhou, Q., Zhang, Z., Luo, L., & Ge, L	2023	China	5,965 ICU patients	3,832 M, 2,133 F	Inclusion: Adults ≥ 18 years with acute myocardial infarction admitted to ICU. Exclusion: History of renal failure, < 24 h ICU stay, missing BUN/Cr data	A retrospective cohort study was conducted using the ICU database with multivariable cox regression and Kaplan–Meier survival analysis	BUN/Cr; measured in the first 24 h of ICU admission; if measured multiple times, the first value was collected	Adjusted for age, sex, ethnicity, BMI, heart rate, high- and low-density lipoproteins, alanine transaminase, acute myocardial infarction category, coronary artery bypass grafting, heart failure, history of diabetes, history of hypertension, and percutaneous coronary intervention	In-hospital mortality. Subgroup analysis with acute myocardial infarction subgroups (STEMI vs. non-STEMI)	1. UCR ≥ 18 (identified as inflexion point) was associated with significantly increased in-hospital mortality in non-STEMI patients compared to UCR < 18 (HR: 1.34, 95% CI: 1.17-1.54, p < 0.05 2. Subgroup analysis showed BUN/Cr ≥ 18 was only associated with in-hospital mortality in patients with non-STEMI and not in patients with STEMI

Table 2 (continued)

Title	Author(s)	Year	Country	Population & Sample Size	Sex Distribution	Inclusion/ Exclusion Criteria	Methodology	UCR	Covariates Included	Outcome Measures	Key Findings
Association of hydration status and in-hospital mortality in critically ill patients with ischemic stroke: Data from the MIMIC-IV database [58]	Wen, J., Hao, X., Pang, J., Li, X., Chen, C., Sun, M., Geng, S., Wang, B., & Jiang, C	2024	China	1,539 ICU patients with ischemic stroke	760 = M, 779 = F	Inclusion: ICU patients from the MIMIC-IV database, first ICU admission with ischemic stroke, age ≥ 18. Exclusion: Prior ICU admissions, malignant tumours, end-stage renal disease, missing data BUN/Cr	Retrospective cohort study utilising MIMIC-IV database; multivariate Cox regression, Kaplan–Meier survival curves	BUN/Cr, (mg/mL: mg/mL); lowest collected values within 24 h of admission to ICU	Adjusted for age, sex, race/ethnicity, MAP, GCS, APSIII, SAPSII, OASIS, congestive heart failure, renal disease	In-hospital mortality	1. UCR ≥ 21.6 was associated with a 61% higher in-hospital mortality (HR: 1.61, 95% CI: 1.16–2.23) compared to UCR < 15.5 2. Every 10-unit increase in UCR was associated with a 29% rise in in-hospital mortality (HR: 1.29, 95% CI: 1.13–1.47)

Table 2 (continued)

Title	Author(s)	Year	Country	Population & Sample Size	Sex Distribution	Inclusion/ Exclusion Criteria	Methodology	UCR	Covariates Included	Outcome Measures	Key Findings
Blood urea nitrogen to creatinine ratio is associated with in-hospital mortality among critically ill patients with cardiogenic shock [82]	Sun, D., Wei, C., & Li, Z	2022	China	1,137 patients with cardiogenic shock	663 = M, 474 = F	Inclusion: ICU patients from the MIMIC-III database, cardiogenic shock based on the international classification of diseases-9 codes or systolic blood pressure < 90 mmHg, and aged ≥ 18. Exclusion: Missing data > 10%, extreme values outside ± 3 SD	Retrospective cohort study using the MIMIC-III database. Multivariable Cox regression, and Kaplan–Meier survival analysis	BUN/Cr, (mg/dL: mg/dL); collected first day of admission ICU	Adjusted for age, gender, ethnicity, admission type, APSIII, SAPSII, using MCS, mechanical ventilation, RRT, Inotropes, vasopressors, vasopressin, mean heart rate, mean blood pressure, and history of chronic heart failure, cardiac arrhythmias, pulmonary circulation disease, hypertension, diabetes, renal disease, liver disease	In-hospital mortality	1. High UCR (≥ 20 compared to < 20) was associated with significantly improved in-hospital survival for patients with cardiogenic shock (HR: 0.66, 95% CI: 0.51–0.84, p < 0.01) 2. The association remained consistent in subgroups with and without acute kidney injury (AKI), AKI HR: 0.72 (95% CI: 0.53–0.97, *P* = 0.03), non-AKI HR: 0.57 (95% CI: 0.35–0.95, p – 0.03) 3. Authors suggest that elevated UCR may reflect neurohormonal activation, which may enhance organ perfusion in the context of cardiogenic shock, contributing to the observed survival benefit

Table 2 (continued)

Title	Author(s)	Year	Country	Population & Sample Size	Sex Distribution	Inclusion/ Exclusion Criteria	Methodology	UCR	Covariates Included	Outcome Measures	Key Findings
Blood urea nitrogen to creatinine ratio is associated with in-hospital mortality in critically ill patients with venous thromboembolism: a retrospective cohort study [59]	Puri, A., Giri, M., Huang, H., & Zhao, Q	2024	China	2,560 ICU with venous thrombo-embolism	1,420 M, 1,140 F	Inclusion: ICU patients from the MIMIC-IV database, diagnosed with venous thrombo-embolism, aged ≥ 18, with available BUN and creatinine data. Exclusion: ICU stay < 24 h, missing data > 20%, multiple ICU admissions	Retrospective cohort study using data from the MIMIC-IV database. Multivariable logistic regression analysis and Kaplan–Meier survival analysis.)	BUN/Cr (mg/dL: mg/dL*); collected first day of admission to the ICU. The average value was used if a variable was assessed multiple times on the first day of admission	Adjusted for age, hemoglobin, WBC, glucose, mean corpuscular hemoglobin concentration, RDW, hematocrit, bicarbonate, international normalized ratio, diabetes, congestive heart failure, coronary artery disease, renal disease, malignant cancer, cerebrovascular disease, mechanical ventilation, diuretic use, and RRT	In-hospital mortality	1. The optimal cut-off of UCR to predict in-hospital mortality was identified as 26.85 BCR ≥ 26.84 compared to < 26.84 was associated with a higher risk of in-hospital mortality (HR = 1.7777; 95% CI: 1.4016–2.2547) 2. High UCR was an independent predictor of mortality in both patients with deep vein thrombosis ($p < 0.001$) and pulmonary embolism ($p = 0.039$) 3. Patients with higher UCR (> 26.84) levels compared to lower UCR levels were more likely to have comorbid diseases ($p < 0.05$)

Table 2 (continued)

Title	Author(s)	Year	Country	Population & Sample Size	Sex Distribution	Inclusion/ Exclusion Criteria	Methodology	UCR	Covariates Included	Outcome Measures	Key Findings
Bun/creatinine ratio and the inferior vena cava collapsibility index in ventilator-associated pneumonia: Caval index in ventilator-associated pneumonia [83]	Karatas, A., Canakci, E., & Yildiz, I	2019	Turkey	57 patients with ventilator-acquired pneumonia	30 = M, 27 = F	Inclusion: ICU patients with ventilator-acquired pneumonia diagnosed via clinical and bacterial criteria stay > 120 h. Exclusion: Patients with human immunodeficiency virus, malignancy, or < 48 h of mechanical ventilation	Prospective cohort study, Spearman's correlation coefficients (correlation between variables), binary logistic regression analysis (mortality)	BUN/Cr; time of collection not specified	Not reported	In-hospital mortality, modification of diet in renal disease and inferior vena cava collapsibility index	1. UCR elevation was not correlated with mortality (no p-value reported) 2. A statistically significant, weak negative association was found between UCR and SOFA score (r = −0.308, $P = 0.020$). The association between UCR and APACHE II was not significantly significant (r = −0.088, $p = 0.515$) 3. There was a statistically significant relationship and a weak positive correlation between the inferior vena cava collapsibility index and UCR (r = 0.325 $P = 0.003$) 4. A moderate positive association was found between modification of diet in renal disease and UCR (r = 0.457, $P < 0.001$)

Table 2 (continued)

Title	Author(s)	Year	Country	Population & Sample Size	Sex Distribution	Inclusion/ Exclusion Criteria	Methodology	UCR	Covariates Included	Outcome Measures	Key Findings
Relationship between the Blood Urea Nitrogen to Creatinine Ratio and In-Hospital Mortality in Non-Traumatic Subarachnoid Hemorrhage Patients: Based on Propensity Score Matching Method [84]	Chen, Z., Wang, J., Yang, H., Li, H., Chen, R., & Yu, J	2022	China	961 ICU patients with non-traumatic subarachnoid haemorrhage	423 = M, 538 = F	Inclusion: Patients from the MIMIC-IV database, patients with non-traumatic subarachnoid haemorrhage, UCR available within 24 h of ICU admission Exclusion: ICU stay < 24 h, pre-existing renal failure, or incomplete data	Retrospective cohort study using data from the MIMIC-IV database. Propensity score matching and multivariable logistic regression analysis.	BUN/Cr, (mg/dL: mg/dL): collected in the first 24 h of being admitted to the ICU	Adjusts for age, sex, ethnicity, myocardial infarction, congestive heart failure, renal disease, mild liver disease, diabetes, sepsis, HR, RR, platelet count, WBC, anion gap, bicarbonate levels, chloride levels, sodium levels, INR, PT, APTT, OASIS, GCS, WFNS, and SOFA	In-hospital mortality	1. The optimal cut-off value for UCR was determined at 27.208. A high UCR (≥ 27.208) was significantly associated with increased in-hospital mortality compared to a lower UCR < 27.208 (OR = 3.783, 95% CI: 1.959–7.305, $p < 0.001$). This remained substantially higher after propensity score matching

Table 2 (continued)

Title	Author(s)	Year	Country	Population & Sample Size	Sex Distribution	Inclusion/ Exclusion Criteria	Methodology	UCR	Covariates Included	Outcome Measures	Key Findings
The association of Blood Urea Nitrogen to Creatinine Ratio and the Prognosis of Critically Ill Patients with Cerebral Infarction: A Cohort Study [85]	Chen, T., Li, A.-P., Gong, Q., Zhou, L., Zhao, Y.-X., Zhou, Z.-W., & Zhou, W.-S	2022	China	2,778 ICU patients with cerebral infarction	Not specified	Inclusion: Patients from MIMIC-III or IV database, cerebral infarction. Exclusion: Age < 18, ICU stay < 24 h, missing data on BUN/Cr	A retrospective cohort study was conducted based on data from the MIMIC-III and MIMIC-IV databases. Propensity score matching, multivariable logistic regression analysis	BUN/Cr, (mg/dL: mg/dL); collected in ICU, timing not specified	Multivariable logistic regression analysis adjusted for respiratory failure, malignant cancer, anticoagulation, liver disease, temperature, WBC, RDW percent, glucose, and bicarbonate, CHF, SBP, WBC, RDW, INR, BUN, Cr Subgroup analysis is adjusted for respiratory failure, malignant cancer, anticoagulation, liver disease, temperature, WBC, RDW percent, glucose, and bicarbonate, BUN, Cr	In-hospital mortality	1. BUN/Cr weakly correlated with increased in-hospital mortality in cerebral infarction patients (RR = 1.01, 95% CI: 1.01–1.02) 2. In subgroup analysis, UCR was only associated with in-hospital mortality in males (RR = 1.02, 95% CI: 1.01–1.04) and not in females ($p > 0.05$). No significant effect of UCR on in-hospital mortality was identified in patients < 65 or ≥ 65 years

Table 2 (continued)

Title	Author(s)	Year	Country	Population & Sample Size	Sex Distribution	Inclusion/ Exclusion Criteria	Methodology	UCR	Covariates Included	Outcome Measures	Key Findings
The association of blood urea nitrogen-to-creatinine ratio and in-hospital mortality in acute ischemic stroke patients with atrial fibrillation: data from the MIMIC-IV database [39]	Li, B., Li, J., Meng, X., Yang, S., Tian, F., Song, X., & Liu, J	2024	China	856 patients with acute ischemic stroke and atrial fibrillation	390 = M, 466 = F	Inclusion: initial ICU admission, diagnosed with both acute ischemic stroke and atrial fibrillation, ≥ 18 years. Exclusion: ICU stay < 24 h or missing UCR data	Retrospective cohort study using the MIMIC-IV database. Multivariable logistic regression models and restricted cubic splines	BUN/Cr collected first day of ICU admission	Adjusted for age and gender, LOS hospital, DBP, MBP, temperature, Spo2, WBC, platelets, anion gap, INR, chronic pulmonary disease, malignant cancer, severe liver disease, OASIS, Charlson Comorbidity Index, peripheral vascular disease, cerebral edema, tracheal intubation, thrombolysis, statins, antiplatelet agents, and anticoagulant drugs	In-hospital mortality	1. Patients in the highest tertile of BUN/Cr (> 22.41) had significantly higher in-hospital mortality compared to patients in the middle tertile (UCR 17.2–22.41) (OR 2.02, 95% CI 1.26–3.26, p = 0.004) 2. A non-linear J-shaped relationship between BUN/Cr and in-hospital mortality was observed (p = 0.027), with a turning point at 19.63 mg/dL 3. A 4% increase in in-hospital mortality was observed for each 1 mg/dL increase in UCR above 19.63 (OR 1.04, 95% CI 1.01–1.06, p = 0.012)

Table 2 (continued)

Title	Author(s)	Year	Country	Population & Sample Size	Sex Distribution	Inclusion/ Exclusion Criteria	Methodology	UCR	Covariates Included	Outcome Measures	Key Findings
The fallacy of the BUN: Creatinine ratio in critically ill patients [72]	Rachoin, J.-S., Daher, R., Moussallem, C., Milcarek, B., Hunter, K., Schorr, C., Abboud, M., Henry, P., & Weisberg, L. S	2012	USA	1,010 patients (derivation cohort), 10,228 (validation cohort)	606 = M, 404 = F (derivation cohort), 5932 = M, 4296 = F (validation cohort)	Inclusion: ICU patients, > 18 years, with available BUN and creatinine measurements. Exclusion: Patients already receiving RRT prior to ICU admission	A retrospective observational study with both a derivation and validation cohort, multivariable logistic regression and Kaplan–Meier survival curves (log-rank test)	BUN/Cr (mg/dL: mg/dL); Derivation cohort measured from ICU days 1–3; Validation cohort used the highest UCR in the first 24 h of ICU stay	Not reported. Stepwise selection of following risk factors: gender (female), race (Caucasian versus other), APACHE II score, use of vasopressors, use of mechanical ventilation, diabetes mellitus, CKD, CHF, HTN and COPD	In-hospital mortality and RRT < 30 days of ICU admission	1. An UCR > 20 compared to < 20 was significantly associated with increased in-hospital mortality (HR: 1.5; 95% CI: 1.3–1.6) and a lower likelihood of RRT in all patients (OR: 1.6 (95% CI: 1.4–1.8)) 2. Patients with a UCR > 20 were more likely to be female, older, and white and to have higher APACHE II scores
	Overall mortality										
Catabolism highly influences ICU-acquired hypernatremia in a mainly trauma and surgical cohort [51]	Rugg, C., Woyke, S., Ronzani, M., Markl-Le Levé, A., Spraider, P., Loveys, S., Schmid, S., Kreutziger, J., & Ströhle, M	2023	Austria	994 ICU trauma and surgical patients	461 = M, 533 = F	Inclusion: ICU traumatological and other surgical patients, ICU stay ≥ 4 days. Exclusion: Patients requiring continuous renal replacement therapy (RRT), ICU stay < 4 days, hypernatremia at admission or hyponatremia (< 130 mmol/L) during ICU stay	Retrospective, single-centre cohort study. Generalised additive models	Urea/Cr, (mg/dL: mg/dL); collected daily from ICU admission till discharge	Analysis adjusted for age, sex, disease severity on admission, degree of catabolism and the development of hypernatremia during ICU stay	Hypernatremia and mortality	1. The adjusted HR for area under the UCR curve > 75 and mortality was not significant per 10 mg*d/dl increase (HR = 1.002, 95% CI: 0.997–1.008, p = 0.495) 2. A higher UCR was observed in patients with prolonged and late hypernatremia (p < 0.001)

Table 2 (continued)

Title	Author(s)	Year	Country	Population & Sample Size	Sex Distribution	Inclusion/ Exclusion Criteria	Methodology	UCR	Covariates Included	Outcome Measures	Key Findings
Prediction of prognosis in patients with nontraumatic intracranial haemorrhage using blood urea nitrogen-to-creatinine ratio on admission: a retrospective cohort study based on data from the medical information Mart for intensive care-IV database [38]	Chen, P., Jiang, Y., Cai, J., Fan, H. Y., Liang, J., Yuan, R., Wu, H., Wang, Y., Cheng, S., & Zhang, Y	2024	China	3,069 patients with non-traumatic intracranial haemorrhage	1,640 = M, 1,429 = F	Inclusion: ICU patients from the MIMIC-IV database with nontraumatic intracranial haemorrhage. Exclusion: Patients < 18 years, ICU stay < 24 h	Retrospective cohort study from MIMIC-IV database, two-piecewise regression model	BUN/Cr (mg/dL: mg/dL); initial values within the first 24 h after admission to the ICU	Adjusted: age, gender, race, CKD, HTN, cerebral infarction, myocardial infarction, diabetes, malignant cancer, CHF, GCS, HR, RR, temperature, systolic blood pressures, Oxygen saturation, lymphocytes, monocytes, neutrophils, white blood cell, red blood cell, platelet, INR	30-day and 1-year mortality	1. U-shaped relationship between UCR and mortality with inflection points at 10.455 for 30-day mortality and 16.25 for 1-year mortality 2. For 30-day mortality (inflection point 10.455) per 1 unit increment of UCR, the mortality rate decreased by 17.7% (OR 0.823, 95% CI: 0.705–0.960) and increased by 1.6% (OR 1.016, 95% CI: 1.000–1.031) on the left and right sight, respectively 3. For 1-year mortality (inflexion point 16.25) per 1 unit increment of UCR, the mortality rate decreased by 5.3% (OR 0.947, 95% CI: 0.899–0.999) and increased by 3.6% (OR 1.036, 95% CI: 1.019–1.054) on the left and right sight, respectively

Table 2 (continued)

Title	Author(s)	Year	Country	Population & Sample Size	Sex Distribution	Inclusion/ Exclusion Criteria	Methodology	UCR	Covariates Included	Outcome Measures	Key Findings
Relationship between blood urea nitrogen-to-creatinine ratio at hospital admission and long-term mortality in patients with acute decompensated heart failure [40]	Murata A, Kasai T, Matsue Y, Matsumoto H, Yatsu S, Kato T, et al	2018	Japan	557 patients with acute decompensated heart failure	361 = M, 196 = F	Inclusion: Cardiac ICU patients, acute decompensated heart failure, UCR data. Exclusion: Patients with dialysis, recent surgery, or life-threatening malignancy	Prospective cohort study. Multivariable Cox proportional hazards regression analysis	BUN/Cr, (mg/dL:mg/dL); collected at time of initial hospital admission	Not reported	Long-term all-cause mortality during a median follow-up of 1.9 years	1. Patients with a high BUN/Cr ratio (≥ 20.4 compared to < 20.4) at admission showed significantly higher long-term mortality (HR 1.81, 95% CI 1.16–2.80, p = 0.009) 2. A dose-dependent relationship between UCR and mortality was observed. The greater the UCR, the greater the risk of all-cause mortality
Urea to creatinine ratio as a predictor of persistent critical illness [25]	Statlender, L., Shochat, T., Robinson, E., Fishman, G., Hellerman-Itzhaki, M., Bendavid, I., Singer, P., & Kagan, I	2024	Israel	2098 ICU patients	PCI Group: 324 = M 156 = F; Non-PCI group: 990 = M, 628 = F	Inclusion: ICU patients Exclusion: Patients who died within 10 days, were admitted with creatinine > 4 mg/dL, and were treated with RRT during ICU stay	Retrospective single-centre cohort study. Patients were grouped based on ICU length of stay, > 10 days (persistent critical illness; PCI group) or not (no-PCI group)	Urea/Cr, (mg/dL: mg/dL); collected the first lab result from each ICU day	The Tukey–Kramer adjustment was used to deal with multiple comparisons in said model	90-day and 1-year mortality	UCR was associated with 1-year mortality, with higher UCR (divided into quintiles) linked to higher 1-year mortality. UCR range 7.69–40; 7.4%, 40.09–56.10; 16.5%, 36.19–75.95; 25.1%, 75–103.33; 30.1%, 103.39–295.45; 43.2%

Overview of studies that have examined the role of UCR (urea-to-creatinine ratio) and its relationship with in-hospital and overall mortality. The table focuses on UCR and the most relevant inclusion and exclusion criteria; other possible study outcomes unrelated to UCR are not described. The table reports whether the studies used blood urea nitrogen to creatinine (BUN/Cr) ratios or urea-to-creatinine ratios, both of which are encompassed under the term UCR. Furthermore, in the event of a reported value, the unit of measurement utilised in the UCR is explicitly stated (mg/dL: mg/dL or mmol/L: mmol/L). For details regarding unit conversion, see Fig. 4. *AKI* acute kidney injury, *APACHE (II)* acute physiology and chronic health evaluation (II), *APSIII* acute physiology score III, *APTT* activated partial thromboplastin time, *ARDS* acute respiratory distress syndrome, *BMI* body mass index, *BUN* blood urea nitrogen, *BUN/Cr* BUN-to-creatinine ratio, *CCI* Charlson comorbidity index, *CHF* congestive heart failure, *CI* confidence interval, *CKD* chronic kidney disease, *COPD* chronic obstructive pulmonary disease, *Cr* creatinine, *DBP* diastolic blood pressure, *ECI* elixhauser comorbidity index, *eGFR* estimated glomerular filtration rate, *F* female, *GCS* glasgow coma scale, *HB* haemoglobin, *HR* hazard ratio/heart rate, *HTN* hypertension, *ICU* intensive care unit, *INR* international normalized ratio, *KDIGO* kidney disease improving global outcomes, *LOS* length of stay, *MAP* mean arterial pressure, *MBP* mean blood pressure, *M* male, *MCS* mechanical circulatory support, *MIMIC* medical information mart for intensive care, *NEUT* neutrophil count, *OASIS* Oxford acute severity of illness score, *OR* odds ratio, *OSI* onychomycosis severity index, *PCI* persistent critical illness, *PT* prothrombin time, *RDW* red blood cell distribution width, *Ref* reference, *RR* relative risk/respiratory rate, *RRT* renal replacement therapy, *RTS* revised trauma score, *SAPSII* simplified acute physiology score II, *SBP* systolic blood pressure, *SD* standard deviation, *SOFA* sequential organ failure assessment, *Spo2* saturation of percutaneous oxygen, *STEMI* ST-elevation myocardial infarction, *UCR/Urea/Cr* urea-to-creatinine ratio, *WBC* white blood cell count, *WFNS* world federation of neurosurgical societies

*The article mentions creatinine in ng/dL, but it was assumed that mg/dL was intended

Table 3 Summary of included articles assessing the relation between UCR and protein intake in critically Ill patients

Title	Author(s)	Year	Country	Population & Sample Size	Sex Distribution	Inclusion/ Exclusion Criteria	Methodology	UCR	Outcome Measures	Key Findings
Association between urea trajectory and protein dose in critically ill adults: a secondary exploratory analysis of the effort protein trial (REEFFORT) [19]	Haines, R. W., Prowle, J. R., Day, A., Bear, D. E., Heyland, D. K., & Puthucheary, Z	2024	Canada/UK	1,277 ICU patients	509 = M, 768 = F	Inclusion: ICU patients ≥ 18 years, mechanically ventilated for > 48 h, and at high nutritional risk (included in EFFORT trial). Exclusion: Patients with missing data or single urea measurements	Secondary exploratory analysis of the EFFORT protein trial: a multicenter RCT comparing the effects of high protein intake (≥ 2.2 g/kg/day) versus low protein intake (≤ 1.2 g/kg/day) on time to discharge alive from the hospital and 60-day mortality in ICU patients	Urea/Cr (mmol/L:mmol/L); collected every ICU day for 12 days,	30-day mortality	1. Higher protein doses (2.2 g/kg/day) resulted in a greater rise in UCR over time 2. A two-fold increase in urea was associated with a higher risk of death at 30 days (HR: 1.34, 95% CI 1.21–1.48) 3. The increased mortality risk in patients randomised to a higher protein was estimated to be mediated by increased urea cycle activity

Table 3 (continued)

Title	Author(s)	Year	Country	Population & Sample Size	Sex Distribution	Inclusion/ Exclusion Criteria	Methodology	UCR	Outcome Measures	Key Findings
Catabolism in Critical Illness: A Reanalysis of the REducing Deaths due to OXidative Stress (REDOXS) Trial [42]	Haines, R. W., Fowler, A. J., Wan, Y. I., Flower, L., Heyland, D. K., Day, A., Pearse, R. M., Prowle, J. R., & Puthucheary, Z	2022	Canada	1,223 ICU patients	715 M, 508 F	Inclusion: ICU patients requiring mechanical ventilation, aged ≥ 18, ≥ 2 organ failures, surviving to day 7. Exclusion: Patients with pre-existing chronic conditions affecting metabolism	Reanalysis of a multicenter RCT of glutamine supplementation ICU patients: REducing Deaths due to OXidative Stress (REDOXS). Multivariable analyses for mortality were adjusted for age, kidney replacement therapy, Sequential Organ Failure Assessment, protein [g/kg/d] received, kidney dysfunction, and glutamine randomization). The marginal structural model was furthermore adjusted to time varying organ failure count including kidney replacement therapy, vasopressor requirement, and mechanical ventilation	Urea/Cr; collected closest to day 7 of ICU admission	30-day follow-up	1. The UCR at day 7 of ICU admission was found to mediate the effect observed between death and glutamine supplementation (Hazard ratio (HR): 1.20; 95% CI, 1.04–1.38; p = 0.014), with the direct effect of glutamine eliminated (HR: 0.90; 95% CI, 0.62–1.30; p = 0.566) 2. A higher time-varying UCR was associated with increased mortality (HR: 2.15; 95% CI 1.66–2.82). This association persisted during the 30-day follow-up period

Overview of studies that have examined the effect of a protein intervention on UCR (urea-to-creatinine ratio) responses during critical illness. The table focuses on UCR and the most important inclusion and exclusion criteria; other possible study outcomes unrelated to UCR are not described. The table reports whether the studies used blood urea nitrogen to creatinine (BUN/Cr) ratios or urea-to-creatinine ratios, both of which are encompassed under the term UCR. Furthermore, in the event of a reported value, the unit of measurement utilised in the UCR is explicitly stated (mg/dL: mg/dL or mmol/L:mmol/L). For details regarding unit conversion, see Fig. 4. *F* female, *HR* hazard ratio, *ICU* intensive care unit, *M* male, *RCT* randomized controlled trial, *REDOXS trial* REducing deaths due to oxidative stress trial, *Urea/Cr/UCR* urea-to-creatinine ratio

circumference during or after ICU stay was not followed up on [26].

A study in 1388 ICU patients observed that patients with overweight (BMI ≥25 kg/m^2) exhibited lower net protein catabolism (reduced net nitrogen loss and reduced UCR on ICU day 5) than matched lean patients (BMI <25 kg/m^2)[27]. Furthermore, sex differences may play a role, with a study in 73 critically ill burn patients showing a significant correlation between UCR and duration of ICU stay in female patients only [28]. A study by Zijlstra et al. in ICU patients with an ICU stay of ≥28 days also observed that the UCR is consistently higher in women than in men [12]. In line with the study by Haines et al. [14], studies indicate that UCR possibly increases during ICU stay, with patients having a prolonged ICU stay showing a greater increase in UCR compared to those with a shorter ICU duration [10, 12, 14, 29]. Notably, Zijlstra et al. also observed that the increase in UCR appears to be most pronounced 7–10 days after ICU admission, after which it gradually increases further [12]. This study showed that both plasma and urinary UCR increased throughout the entire ICU stay, exhibiting a comparable trajectory.

Rousseau et al. observed in ICU survivors (n= 64) a significant decrease in UCR values at three months post-ICU discharge compared to ICU discharge (p= 0.008), paralleling serum short chain acylcarnitine levels that are indicative of impaired protein metabolism [30]. An increase in the sarcopenia index, an index of skeletal muscle mass (ratio between serum creatinine and serum cystatin C), accompanied this observation. Moreover, in a study of long-term mechanically ventilated patients, UCR was related to long-term clinical outcomes. Patients who successfully weaned from invasive mechanical ventilation (n= 205) exhibited a lower UCR at 6 weeks of ventilator dependency compared to those who remained ventilator-dependent or had died (n= 190; 28.7 vs 35.9, p= 0.001)[31].

UCR and ICU admission

In addition to the UCR-related observations during ICU stay and post-ICU recovery, several studies have assessed the predictive value of UCR to become admitted to the ICU. A retrospective study demonstrated that UCR exhibits moderate predictive performance for the likelihood of ICU admission in emergency department patients (n= 914), with an AUC of 0.61 [95% CI: 0.58–0.64] and an optimal predictive value of 23.64 [32]. A tendency for UCR to predict the likelihood of ICU admission by 6% for each 5-unit UCR increase was observed (HR 1.06, 95% CI: 0.99–1.12, p= 0.085)[33]. Furthermore, a single-centre, retrospective case–control study among 95 adult COVID-19 patients also demonstrated that UCR was an independent predictor of admission to an ICU (Odds Ratio =1.72, 95% CI 1.20–2.66)[34]. However, this was not applicable to hospitalised patients with chronic kidney disease [35]. Additionally, UCR has been linked to disease severity, as demonstrated by a retrospective Indian study of hospitalised COVID-19 patients (n= 996), which found higher UCR levels in severe cases compared with mild cases (clinical severity classified according to peripheral oxygen saturation; AUC 0.62, 95% CI 0.56–0.67, optimal cut-off 14.5)[36].

UCR and mortality in critically Ill patients

Seventeen studies have examined the association between UCR and mortality (see Table 2). Forest plots were generated to summarise the association between UCR and in-hospital mortality across studies included in the meta-analysis (Figs. 1 and 2). The forest plots for unadjusted relative risks (RR) exhibited higher in-hospital mortality in the higher UCR group (RR =1.53, 95% CI: 1.16, 2.03). However, this trend diminished with adjusted hazard ratios (HR), where UCR was incorporated in multivariable Cox regression models (adjusted HR =1.25, 95% CI: 0.77, 2.01). Additionally, several studies have indicated that the relationship between UCR and in-hospital mortality may not be linear. Both low and high UCR have been observed to be associated with an elevated risk of in-hospital mortality, indicating a U-shaped association [37–39].

Furthermore, an association between UCR and long-term all-cause mortality is described in two studies. A high UCR (≥ 20.4) on hospital admission in cardiac ICU patients (n= 557) was associated with an increased likelihood of long-term mortality (HR 1.81, 95% CI 1.16–2.80, p= 0.009) in a retrospective analysis [40]. A single-centre retrospective study also demonstrated that an elevated UCR at ICU admission was associated with an increased mortality risk within one year after ICU admission in 2098 patients that survived until at least the 10 th day of ICU and did not require renal replacement therapy (RRT). This association was observed consistently across increasing quintiles, with progressively lower survival rates [25].

UCR and Protein Intake during critical illness

Multiple studies indicate that UCR could be responsive to nutritional interventions in critically ill patients (Table 3). A secondary analysis of the EFFORT protein trial revealed that high protein doses (> 2.2 vs 1.2 g/kg/day) were harmful in patients with high sequential organ failure (SOFA)-scores and renal impairment [41], and were associated with elevated urea levels [19]. More profound ureagenesis was related to increased mortality at 30 days, even after adjustment for organ dysfunction

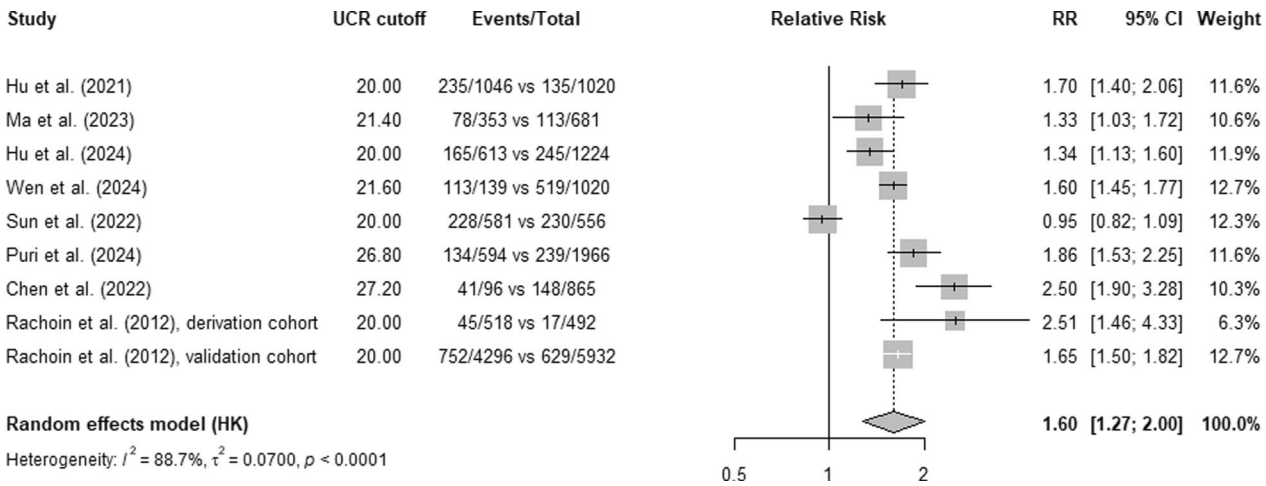

Fig. 1 Forest plot of relative risk for in-hospital mortality. The illustration depicts forest plots derived from a meta-analysis conducted with a random-effects model. The degree of heterogeneity was evaluated using the I^2 statistic. The UCR cut-off values were retained as reported in the original studies, with the value closest to 20 (BUN:C, mg/dL:mg/dL) chosen for comparison with other studies. This figure illustrates unadjusted relative risks based on the number of in-hospital mortality events in the low and high UCR groups

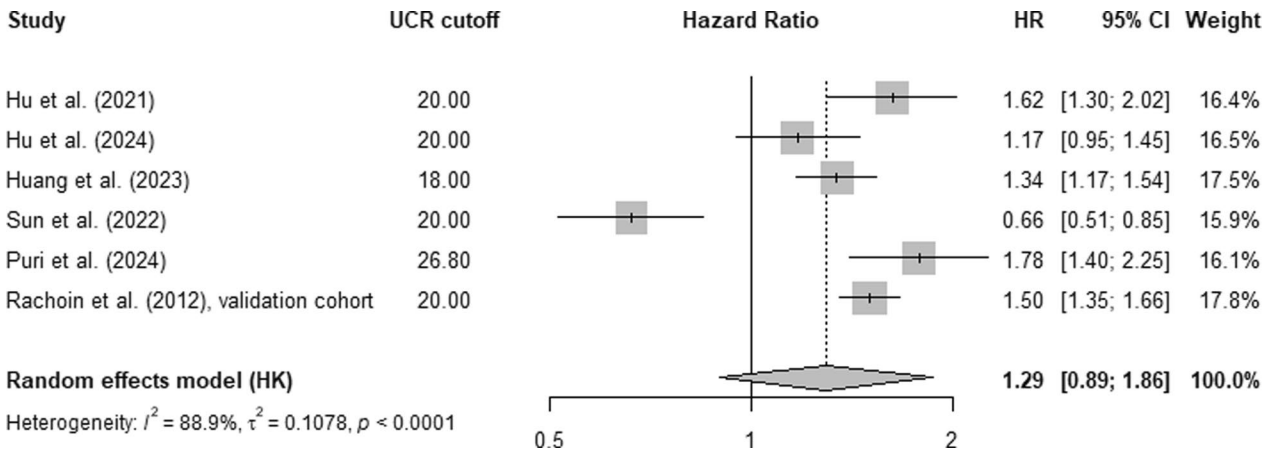

Fig. 2 Forest plot of hazard risk for in-hospital mortality. The illustration depicts forest plots derived from a meta-analysis conducted with a random-effects model. The degree of heterogeneity was evaluated using the I^2 statistic. The UCR cut-off values were retained as reported in the original studies, with the value closest to 20 (BUN:C, mg/dL:mg/dL) chosen for comparison with other studies. This figure illustrated adjusted hazard ratios based on multivariable Cox regression models. Covariates adjusted for in the multivariable models are presented in Table 2

and acute kidney injury (AKI)[19]. A comparable urea-mediated correlation was also identified in a reanalysis of the multicentre randomised trial to investigate the efficacy of glutamine supplementation during critical illness (REDOXS trial) [42]. The findings indicated that an elevated UCR trajectory was particularly prominent in patients randomized to glutamine and linked to poorer survival. The UCR, measured around day 7, was associated with an increased risk of death while no longer a direct impact of glutamine supplementation on mortality was identified after adjustment. These findings indicate that an elevated UCR may be indicative of harm from high protein doses or amino acid supplementations during critical illness.

The UCR was also included in secondary analyses of other feeding interventions. A pre-specified analysis of the Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients (EPaNIC) study showed that early parenteral nutrition (PN) compared to late supplemental PN (initiation after 1 week) resulted in a notable elevation in UCR levels and higher nitrogen loss from day 4 to day 11 of ICU stay [15]. The additional nitrogen loss net wasted in ureagenesis attributable to early parenteral nutrition was estimated to be 30%

after one week and 63% by day 14. A less negative nitrogen balance was observed with late PN, suggesting that delayed PN was more effectively utilised when provided in the later days of ICU stay. UCR was thereby indicative of 'feeding responsiveness'. Another study demonstrated that continuous feeding resulted in a steeper positive gradient of UCR compared to bolus feeding over 10 days of nutrition after adjusting for several covariates, including RRT and protein amount delivered ($p = 0.016$)[43]. This finding could indicate that bolus feeding induces a more pronounced anabolic response than continuous feeding, a phenomenon referred to as 'the muscle full effect', which posits that the body has an upper limit for the amount of amino acids used for muscle protein synthesis. In this case, bolus feeding was suggested to prevent protein catabolism compared to continuous feeding, with the UCR being reflective of excess amino acids entering the urea cycle that can no longer be utilised for protein tissue building [44–46].

UCR and other outcomes during critical illness

In addition to its role in catabolism and persistent critical illness, the literature describes other functions of UCR (see Additional file 1: Table S3). For example, an elevated UCR at the time of ICU admission (18 and 24.9 as the cut-off value) has been associated with the onset of delirium in critically ill patients and a longer duration of ICU stay [47, 48]. In critically ill patients with aneurysmal subarachnoid haemorrhage, an elevated UCR in the acute phase (days 5–7 after ictus) has been linked to an increased risk of delayed cerebral ischemia (DCI) (UCR > 29), DCI-related infarction (UCR > 30.8), and unfavourable clinical outcomes at 12 months [49].

Discussion

This scoping review and meta-analysis sought to ascertain the significance of the UCR in critically ill patients in relation to mortality and clinical outcomes, as well as to determine whether UCR may serve as a potentially useful marker to reflect protein catabolism during critical illness. UCR was found to substantially increase over time during persistent critical illness among patients with prolonged ICU stays. There is a potential association between admission UCR and in-hospital mortality, although there is considerable heterogeneity across studies. Additionally, it may rather be a biomarker for illness than the cause of mortality. Secondary analyses of two large intervention studies (EFFORT protein and REDOXS) indicate that elevated UCR associates with increased mortality in ICU patients receiving high protein doses or amino acid supplementation, suggesting that the UCR represents a promising catabolic signature and a potential biomarker to monitor the response to nutritional interventions aiming to reduce muscle wasting. Furthermore, additional links between clinical outcomes and UCR were found, including the correlation between elevated UCR and the incidence of delirium and cerebral ischemia in specific patient groups.

Application of UCR in clinical practice

In patients with critical illness, UCR is higher at ICU admission than in healthy controls [50] and increases further during admission [10, 14, 29, 43, 49, 51], with the most pronounced elevation occurring during the initial 7–10 days [12, 43, 51]. This observed increase in ureagenesis during critical illness could be attributed to a decline in amino acid utilisation and an increase in protein breakdown in the body (anabolic resistance), which results in a greater influx of amino acids into the urea cycle [12, 52–54]. After the first 7–10 days, a gradual yet sustained rise of UCR was noted throughout the remainder of the ICU stay [12]. It is conceivable that the lack of further elevation in the UCR can be attributed to the urea cycle's optimal efficacy being reached. The study by Zijlstra et al. demonstrated that both plasma urea and urinary urea excretion rise during the initial ten to fourteen days of ICU stay, potentially indicating an upregulation of the urea cycle in the first week before maximum capacity is reached [12]. Following this interval, a modest decline in both plasma urea and urinary urea excretion was noted, amounting to 1% per day for the remainder of the ICU stay. Consequently, UCR continues to exhibit an upward trend [12], attributed to a more pronounced decrease in creatinine levels in conjunction with a reduction in muscle mass [8, 55]. In this context, an elevated UCR could serve as an indicator of skeletal muscle wasting during persistent critical illness. This finding was also identified by Haines et al., observing a weak converse correlation between dynamics of UCR and muscle CSA on CT scans in trauma patients [13]. Considering the available literature, we recommend UCR to be measured upon ICU admission (as a baseline value) and subsequently at regular intervals, rather than a solitary measurement at admission as has been conducted in the majority of available studies [27, 28, 38, 56–59]. The latter approach may also reflect other causes of UCR elevation beyond catabolism (Fig. 3), while assessing UCR dynamics may be particularly helpful in critically ill patients with prolonged anticipated ICU stays, as a continued rise in UCR may indicate a protein catabolic state and progressive muscle wasting [14, 19, 25].

Furthermore, it is important to consider the potential influence of age and sex differences, with evidence suggesting that the UCR increases with age [60] and may be higher in female than in male ICU patients [12, 28]. This discrepancy could be attributed to differences in

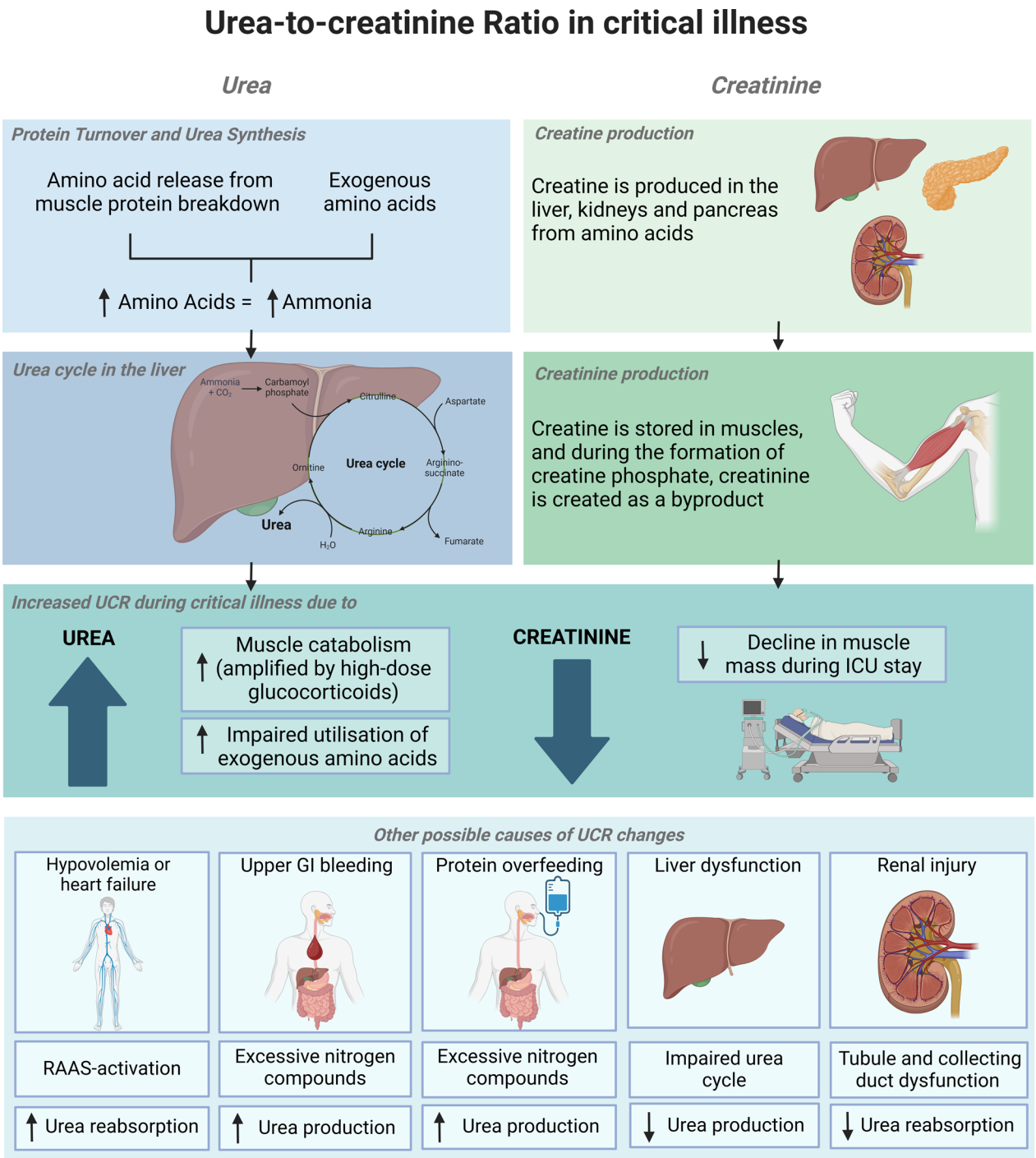

Fig. 3 Urea-to-creatinine ratio during critical illness. The illustration depicts the production and processing of urea and creatinine within the human body. The figure illustrates the potential causes of increased UCR during critical illness and other factors that may contribute to this phenomenon. Abbreviations: ICU = Intensive Care Unit; GI = Gastro-intestinal. Created with Biorender.com

muscle mass proportion, resulting, on the one hand, in less creatinine release, and on the other hand, in a higher risk of protein overfeeding since the current guidelines advise to dose protein irrespective of sex or age (i.e. in grams/kg actual body weight in case of BMI ≤ 25 kg/m^2 instead of measured fat-free mass or sex-adjusted) [61, 62]. The recently conducted PRECISe trial revealed a lower EuroQoL 5-Dimension 5-Level

(EQ-5D-5L) health utility score with higher enteral protein provision (2.0 g/kg/day) compared to standard protein provision (1.3 g/kg/day), which was most pronounced in female patients [63]. The authors hypothesise that this may be due to women's lower lean body mass. It is conceivable that protein dosing based on lean body mass rather than actual body weight might result in less overfeeding and, thus, a less pronounced UCR increase. However, this hypothesis remains to be tested.

A recent review has advocated for further investigation into UCR as a potential marker in response to nutrition provision [64]. Secondary analyses of the EFFORT Protein study [65] and the REDOXS trial [42] demonstrated poor outcomes when patients were provided with high protein and glutamine provision, respectively, which was reflected by an elevated UCR trajectory in the high protein/amino acid intervention. However, it is currently unknown if ureagenesis itself or other toxic metabolites are responsible for impaired outcome associated with protein overfeeding during acute catabolism. It is postulated that if the urea cycle is overloaded through both endogenous (from protein degradation) and exogenous (from protein provision) sources, toxic intermediate metabolites, such as ammonia, cannot be converted and will accumulate, particularly in the critically ill [66]. Hyperammonaemia may present in adult ICU patients independently of liver dysfunction, possibly as a result of redundant protein feeding stressing the urea cycle [67]. Intracellular hyperammonaemia harms several metabolic processes, including skeletal muscle metabolic derangements, impaired skeletal muscle protein synthesis, and increased autophagy, resulting in muscle loss and weakness [68]. Furthermore, hyperammonaemia has been demonstrated to induce alterations in pH, membrane potential, and cell metabolism, which can result in damage to multiple organs [68]. Whether elevations in UCR parallel hyperammonaemia in the critically ill seems logical but remains to be elucidated.

The EAT-ICU study demonstrated that patients who were randomized to receive individualized early goal-directed nutrition exhibited a reduced negative protein balance in comparison to those who received standard nutritional care [69]. However, the group with early goal-directed nutrition exhibited augmented plasma urea and 24-h urinary urea, with the rise in plasma urea closely aligning with the enhanced protein balance [69]. It is recognised that the capacity of critically ill patients to utilise ingested protein for muscle protein synthesis is impaired despite the presence of normal protein digestion and amino acid absorption [17]. This phenomenon is indicative of anabolic resistance. These mechanisms, alongside suppressed autophagy, likely explain why recent large trials observed harmful effects of high protein provision during acute critical illness [16, 20].

Conversely, three studies have indicated a U-shaped relationship between UCR and in-hospital mortality [37–39]. While UCR was assessed in one of these studies at ICU admission and in the remaining the timing was not reported, it is plausible that very low UCR levels may be indicative of inadequate protein intake, which aligns with evidence suggesting that protein intake and mortality exhibit a U-shaped relationship [70]. Consequently, a low or decreasing UCR could indicate an improved response to dietary protein [20], a crucial tipping point from which nutrition or protein provision may be increased. However, nutrition intervention studies incorporating UCR as a biomarker are required to test the hypothesis that UCR is responsive to nutrient provision in order to advance personalised nutrition therapies in the ICU. Furthermore, studies investigating the relationship between UCR and protein metabolism pathways during critical illness are warranted to elucidate the magnitude to which UCR may be related to 'protein-feeding responsiveness'[20].

Pitfalls of UCR as a catabolic biomarker in critical illness

It is important to note that there are certain pitfalls when using UCR as a catabolic biomarker in critical illness in clinical practice (Fig. 3). Firstly, since UCR is a ratio, it is essential to take into account variations in both urea and creatinine when assessing it as a metabolic signature. Furthermore, factors other than pronounced protein catabolism may also increase UCR. These include conditions that enhance urea reabsorption, such as activation the renin-angiotensin activating system (i.e., hypovolemia or heart failure), as well as factors that elevate urea production, such as high dietary protein intake and blood absorption in the gastrointestinal tract [8, 71, 72]. Conversely, the level of UCR can be reduced by liver dysfunction that affects the urea cycle metabolism [73]. Similarly, renal factors, such as medications (e.g. loop diuretics) [74] or damage to the renal tubules [75], may decrease urea reabsorption and lead to a decrease in UCR. The study by Haines et al. found that major trauma patients with severe AKI tended to have a lower UCR [14], while a single-centre retrospective study of ICU patients revealed no significant difference in UCR between patients with disparate AKI stages [25]. Differences in AKI aetiology may explain discrepancies in these findings. One study observed an UCR > 20 at ICU admission, indicative of prerenal insufficiency, to reduce the risk of requiring RRT [72]. In addition to this, evaluating UCR trajectory as a metabolic signature during RRT may be challenging since RRT removes both urea and creatinine from the blood, with a therapy-specific relationship between solute removal and clearance [43, 76]. Future

studies are required to determine suitable catabolism biomarkers for AKI and RRT patients in the ICU, as they represent a challenging population.

Lastly, recognising that the UCR is reported in disparate units is also crucial. In Europe, the urea/creatinine ratio is frequently used, whereas in the United States, the blood urea nitrogen (BUN)/creatinine ratio is commonly reported. Conversion factors are available for calculating BUN, which is approximately one-half (28/60 or 0.446) of blood urea [77]. It is essential to ensure that both BUN or urea and creatinine are reported in the same units to ensure the accuracy of the ratio calculation (Fig. 4). Standardisation in reporting facilitates comparison between studies and provides a uniform approach to assessing patient outcomes and formulating clinical decision-making.

Limitations and strengths

A strength of this review is its comprehensive examination of UCR in the context of critical illness. It offers insights into its potential as a biomarker for muscle wasting, persistent critical illness, and response to nutritional interventions. The review also addresses interpretation challenges and identifies knowledge gaps in critical care. However, several limitations should be noted. First, selective reporting bias is a potential limitation due to the post-hoc nature of our meta-analyses. In addition, the substantial heterogeneity between studies and their study populations, the absence of cut-off values for UCR, and the paucity of studies directly comparing UCR with tracer methodologies or measurements of absolute muscle mass loss impede the ability to derive precise and uniform conclusions. Additionally, there is a risk of publication bias, as unpublished or non-English studies may not be captured in the search, and the majority of included studies are observational and retrospective in nature. Another limitation is the geographical concentration of the included studies, with multiple articles originating from China. This predominance may introduce a regional bias, as healthcare practices and patient demographics may differ between regions. Consequently, this may hamper the generalizability of the findings to other healthcare systems. Lastly,, most of the discussed studies are from single centres, which could further limit the external validity of the results.

Implications for future research

Future studies should focus on refining UCR's clinical applications and tailoring its use to specific critically ill patient groups, as its interpretation must always be context specific. Additional research is warranted to establish optimal cut-offs for rises in UCR related to protein catabolic processes, such as severe muscle wasting, along with consequent investigations exploring its role in guiding nutritional interventions. However, since a strict cut-off approach may fail to accurately capture dynamic changes in UCR over time, future studies should consider incorporating repeated measurements

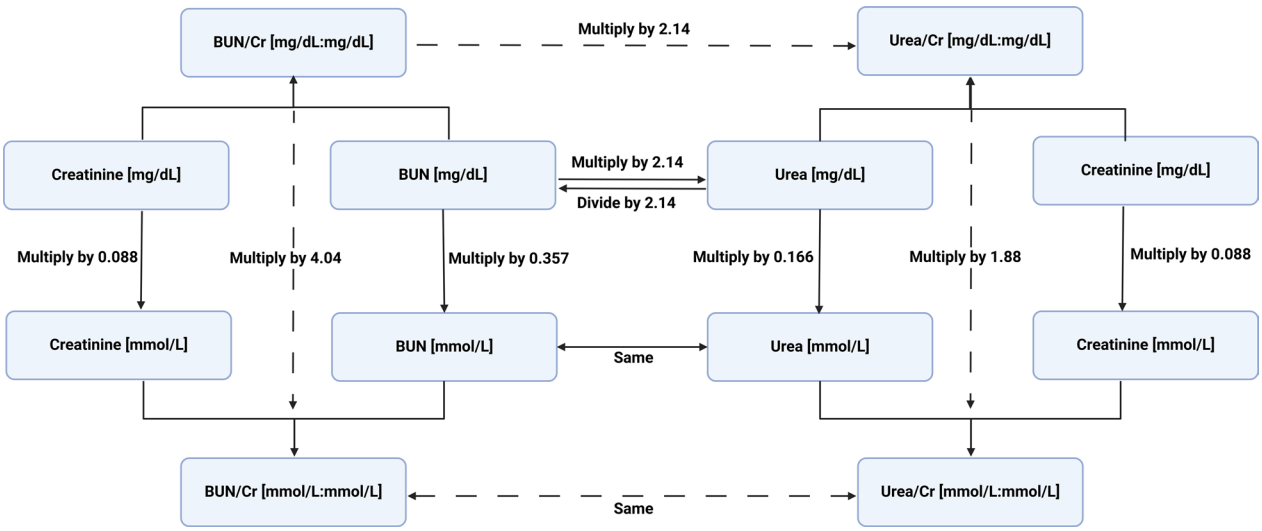

Fig. 4 Conversion factors BUN and urea. The chemical formula of urea is $CO(NH_2)_2$, with a molecular weight of approximately 60 [78]. Each of the two nitrogen molecules has a weight of approximately 14 g/mol. The ratio 60/28 can be expressed as follows: To convert from BUN to urea, one must multiply by 2.14. Similarly, to convert from urea to BUN, one must divide by 2.14. To convert from mg/dL to mmol/L for BUN and urea, the value should be multiplied by the weight in mol and then multiplied by 10 to convert L to dL. For BUN, this is 2 × nitrogen (2 × 14 = 10/28 = 0.357), while for urea it is $CO(NH_2)_2$ (10/60 = 0.166). Both BUN and urea in mmol/L are molecular weight units and can be converted without the use of a conversion factor. All of these values are approximations and have been rounded for simplicity. Created with Biorender.com

or utilizing a continuous ordinal modelling approach. The development of valuable markers to tailor protein provision throughout critical illness remains an unmet need [21]. UCR may represent a promising marker to guide this process, but prospective studies are required to substantiate this hypothesis.

Summary

UCR is potentially reflective of muscle wasting and may be an indicator of persistent critical illness and in-hospital mortality in critically ill patients. A high UCR may indicate an excess of exogenous amino acids provided in addition to endogenous protein catabolism, suggesting that the protein supply may temporarily exceed the body's capacity for utilisation. It is crucial to acknowledge that a multitude of factors can elevate UCR levels beyond the mere phenomenon of protein catabolism. The necessity for valuable markers to tailor protein provision is evident, and the dynamics of UCR in critically ill patients may play an important role in this in the future. However, this approach needs further evidence-based research and warrants confirmation in prospective studies. To ensure the effective application of UCR in clinical practice and to facilitate the guidance of nutritional interventions, it is essential to establish age and sex-specific cut-off values explicitly tailored for critical illness.

Abbreviations

AKI	Acute kidney injury
APACHE	Acute physiology and chronic health evaluation
COVID-19	Coronavirus disease 2019
CSA	Cross-sectional area
CT	Computed tomography
DCI	Delayed cerebral ischemia
EQ-5D-5L	EuroQoL 5-dimension 5-level
ICU	Intensive care unit
KDIGO	Kidney disease improving global outcomes
MIMIC	Medical information mart for intensive care
PCI	Persistent critical Illness
PN	Parenteral nutrition
PRISMA	Preferred reporting items for systematic reviews and meta-analysis
RCT	Randomized controlled trial
REDOXS trial	REducing deaths due to oxidative stress trial
RRT	Renal replacement therapy
SOFA	Sequential organ failure assessment
STEMI	ST-elevation myocardial infarction
UCR	Urea-to-creatinine ratio/BUN-to-creatinine ratio

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-025-05396-6.

Additional file 1: Study flowchart, critical appraisal, summaries of studies on other UCR roles, and exclusion list.OR shorter: online data supplement.

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Author contributions
MCP: Conceptualisation, Methodology, Formal analysis, Writing – original draft/review. MM: Writing – review. AvE: Methodology, Formal Analysis, Writing – review. IWKK: Writing – review. ARHvZ: Conceptualisation, Writing – review. All authors read and approved the final manuscript.

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Availability of data and materials
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Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Conflict of interest
The authors declare no competing interests.

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